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Menstrual Factors and Risk of Breast Cancer

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ABSTRACT

A case control study of 2,908 breast cancer cases and 3,180 controls, derived from a nationwide screening program, enabled evaluation of the relationship of breast cancer risk to a variety of menstrual factors. Risk was significantly inversely related to age at menarche, with women who first menstruated at age 15 or later having a 23% lower risk than those with menarche prior to the age of 12. There was a higher relative risk (1.3) for premenopausal than menopausal women. In contrast to previous studies, there was only a slight increase in risk associated with a late age at natural menopause, possibly owing to errors in recall. Bilateral oophorectomy at an early age exerted a protective influence on breast cancer risk, with effects manifested approximately 10 to 15 years after oophorectomy. Women who had both ovaries removed prior to the age of 40 had a 45% reduced risk compared to women with a natural menopause at ages 50 to 54. In addition, bilateral oophorectomy at an early age was associated with a lowered risk relative to natural menopause at a comparable age, which may reflect the more pronounced and sudden decline in endogenous hormones associated with the surgery. Although these results were based on patient reports regarding the types of surgical menopause experienced, validation against medical records showed close correspondence regarding the number of ovaries removed.

INTRODUCTION

The relationship between menstrual function and breast cancer is well recognized, including increased risks observed among women with early menarche (1) or late menopause (2,3) and the lowered risk among those with an artificial menopause, particularly if the operation involves ovarian ablation at an early age (4,5).

Despite the recognition of these relationships, there continues to be limited understanding regarding the interrelationship of different characteristics of menstrual status, including the correlation of age at menarche with

establishment of regular cycles, the comparative risks associated with varying types of menopause after adjustment for differential ages at menopause, and the effects of latency relating to menstrual events. In addition, most studies have relied on patients' reports of gynecologic surgery to define ovarian status, yet the reliability of such information is unknown. In order to assess more fully the effects of menstrual function on breast cancer risk, we undertook a case control study of breast cancer, obtaining detailed information on menstrual characteristics through personal interviews as well as through validation of this information against hospital discharge and operative records.

METHODS

This case control study involved participants in the Breast Cancer Detection Demonstration Project (BCDDP), a multicenter breast cancer screening program involving over 280,000 women at 29 widely dispersed centers. This program, jointly sponsored by the American Cancer Society and the National Cancer Institute, recruited women between 1973 and 1975 for a 5-year program of annual breast examinations by the combined modalities of clinical examination, mammography, and thermography. Cases consisted of women from 28 centers whose breast cancer was detected during the period January 1973 through November 1980. Control subjects were selected from women who had not received either a recommendation for biopsy or a biopsy during the course of screening participation. The controls were chosen to be comparable to the cases on center, race (white, black, Oriental, other), age (same 5-year age group), time of entry (same 6-month period), and length of continuation in the program (controls had to have as many years of screening as cases).

Home interviews were conducted by trained interviewers during two different periods, namely January 1978 through November 1978 and June 1982 through July 1983. Completed interviews were obtained from 4,351 cases (77.9% of eligible subjects) and 3,583 controls (83.0%). Reasons for nonresponse included subjects being unlocatable or having moved too far away for interviews to be conducted (1.7% of cases vs. 4.3% of controls), refusals (5.0% vs. 7.8%), death (11.5% vs. 2.3%), and other miscellaneous reasons (3.9% vs. 2.6%). Women who were interviewed were not found to differ significantly from those not interviewed with regard to the number of factors determined for each woman at the time of entry to the screening project, including age, race, family income, and history of benign breast surgery.

Menstrual status information included age at menarche, age at onset of regular menstrual cycles, menopause status, type of menopause, age at menopause, and menopausal symptoms. Menarche was defined as the onset of menstruation, while regular cycles were defined as those occurring at predictable intervals. Women were labelled as premenopausal if they reported having had a menstrual period within three months time of breast cancer diagnosis (or equivalent time for controls). Those whose menstrual periods had stopped prior to this time were designated as menopausal, and categorized as to the event causing cessation of menses (natural or surgical). Women who underwent a surgical menopause were further classified according to whether they experienced a hysterectomy, a hysterectomy with unilateral oophorectomy, or a bilateral oophorectomy.

A total of 134 cases and 38 controls reported a history of breast cancer prior to entering the project and were excluded from the present analysis. We also restricted analysis to white subjects (91% of the entire study population). The final study group consisted of 2,908 cases and 3,180 controls.

For evaluating effects of an exposure factor, the measure of association used was the relative risk (RR), as estimated by the odds ratio. Adjustment for confounding variables was accomplished using multivariate logistic techniques (6), deriving maximum likelihood estimates of combined RRs and 95% confidence intervals (CI). Two-tailed tests for trends in the logistic analyses were obtained by categorizing the exposure variable, assigning the score j to the j-th exposure variable, and treating the scored variable as a continuous variable. Since matching was employed in the study design, multivariate analyses using a program for matched data were also undertaken (7). These analyses produced results nearly identical to those derived from the unmatched analyses; the latter analyses have thus been chosen for presentation.

For purposes of validation, a random sample of approximately 25% of the interviewed cases and controls reporting prior gynecologic surgery was chosen. Further information on any operation involving removal of the uterus or ovaries was sought by requesting copies from hospitals where the surgery was performed of operative reports, discharge summaries, and pathology reports. All records were reviewed in order to obtain an accurate assessment of the number of ovaries removed at surgery. Complete information was obtained from 154 of the 234 cases chosen for validation (65.8%) and from 128 of 196 controls (65.3%).

RESULTS

Onset of Menstruation

The relationship between age at menarche and breast cancer risk is shown in Table 1. In the total series of patients, there was a significant decreasing trend in risk ($p < 0.01$) with increasing age at menarche, with those having their first menstrual cycle at 15 years of age or later being at a 23% lower risk than those first menstruating prior to the age of 12. The decreasing trend was similar for breast cancer detected prior to the age of 45 and that diagnosed later. The age-at-menarche effects did not appear to be confounded by other breast cancer risk factors, including a family history of breast cancer, parity, age at first livebirth, history of benign breast disease, weight, or exogenous hormone use.

In addition to information on age at menarche, subjects were questioned about the regularity of their menstrual cycles. A total of 15.7% of the cases and 14.5% of the controls reported having irregular cycles prior to age 25 or their first pregnancy (whichever came earliest), resulting in a RR of 1.1 (95% CI 0.9–1.3) compared to those with regular cycles. Among women whose cycles did become regular (approximately 90% of study subjects), age at menarche and the interval between menarche and regularization were examined in relation to each other and to breast cancer risk. The percentage of control women becoming regular within four years of menarche was slightly, although nonsignificantly, greater for those with early menarche (<13) than for those with later menarche (89.1% vs. 85.9%); this difference was similar when those with menarche prior to age 12 were compared to those with menarche at age 15 or later (87.9% vs. 85.0%).

As shown in Table 2, there was some evidence of a nonsignificant trend in risk with increasing interval between menarche and onset of regular periods. However, the difference in risk between those with 5 or more years between menarche and regularization and women with immediate regularity was only on the order of 20% overall. In addition, no consistent pattern of risk was apparent when timing of regularization was examined within age at menarche categories. Similarly, no significant differences in risks were observed when either age at menarche or the interval to regularization were more finely categorized or when effects were examined according to age at breast cancer diagnosis.

Menopause

A total of 887 (30.5%) of the cases and 868 (27.3%) of the controls reported being premenopausal at the time of breast cancer diagnosis, resulting in an age-adjusted RR of 1.3 (95% CI 1.1–1.5) compared to menopausal women (Table 3). Risks associated with being premenopausal were elevated for every age at diagnosis category less than 55 years of age, and significantly elevated for those aged 45–49 (RR = 1.4) and 50–54 (RR = 1.6).

Among the menopausal women, 58.7% reported a natural menopause and 41.3% a surgical menopause (Table 4). After adjustment for age at diagnosis and years of menopausal hormone use, those with a surgical menopause involving a hysterectomy alone or removal of one ovary were at a nonsignificant 10% excess risk compared to those with a natural menopause. In contrast, women with a bilateral oophorectomy were at slightly lower risk than naturally menopausal women (RR = 0.9). These findings remained unaltered when adjustment was made

Table 1
Relative Risks[a] of Breast Cancer by Age at Menarche and Age at Diagnosis of Breast Cancer

Age at menarche	Age at breast cancer: <45 years Cases	<45 years Controls	<45 years RR	45+ years Cases	45+ years Controls	45+ years RR	Total Cases	Total Controls	Total RR
<12	80	79	1.00	435	414	1.00	515	493	1.00
12	94	99	0.95	613	642	0.91	707	741	0.91
13	114	127	0.88	753	877	0.82	867	1004	0.82
14	30	60	0.49	419	441	0.90	449	501	0.85
15+	26	32	0.82	323	396	0.78	349	428	0.77
Trend test		3.57 (p = 0.06)			5.24 (p = 0.02)			7.90 (p < 0.01)	

[a]Relative risks are adjusted for age at diagnosis. Analysis excludes 21 cases and 13 controls with missing ages at menarche.

Table 2
Relative Risks[a] of Breast Cancer by Years from Menarche to Regular Menstrual Cycles

Age at Menarche	Years from menarche to regular cycles			
	0	1–4	5+	Never
<13	1.00 (885)[b]	0.95 (192)	1.52 (51)	0.92 (67)
13+	1.00 (1125)	1.09 (282)	1.03 (78)	1.20 (134)
Total	1.00 (2010)	1.04 (474)	1.18 (129)	1.10 (201)

[a]Relative risks are adjusted for age at diagnosis. Total relative risks are adjusted additionally for age at menarche. Analysis excludes 94 cases and 87 controls who had missing information on either age at menarche or age at which cycles become regular.
[b]Numbers in parentheses represent number of cases.

Table 3
Relative Risks[a] of Breast Cancer by Menopause Status and Age at Diagnosis

Age at diagnosis	Menopause status	Cases	Controls	RR	(95% CI)
<45	Menopausal	65	83	1.00	—
	Premenopausal	278	314	1.16	(0.8–1.7)
45–49	Menopausal	149	197	1.00	—
	Premenopausal	334	323	1.40	(1.1–1.8)
50–54	Menopausal	391	467	1.00	—
	Premenopausal	240	193	1.56	(1.2–2.0)
55+	Menopausal	1374	1526	1.00	—
	Premenopausal	35	38	1.04	(0.6–1.7)
Total	Menopausal	1979	2273	1.00	—
	Premenopausal	887	868	1.32	(1.1–1.5)

[a]Total relative risk is adjusted for age at diagnosis. Analysis excludes 42 cases and 39 controls with missing information on menopause status.

Table 4
Relative Risks[a] of Breast Cancer Among Menopausal Women by Type of Menopause

Type of menopause	Cases	Controls	RR	(95% CI)
Natural	1119	1299	1.00	—
Hysterectomy	322	350	1.08	(0.9–1.3)
Hysterectomy with unilateral oophorectomy	158	165	1.09	(0.9–1.4)
Bilateral oophorectomy	318	388	0.92	(0.8–1.1)

[a]Relative risks are adjusted for age at diagnosis and years of menopausal hormone use. Analysis excludes premenopausal women (887 cases, 868 controls), those with missing information on menopause or ovarian status (71 cases, 79 controls), and those with missing information on years of menopausal hormone use (33 cases, 31 controls).

for a number of other breast cancer risk factors. In addition, adjustment for smoking status did not appreciably affect the results, although smoking was not a risk factor in this data set (8).

Within each type of menopause, risks were examined according to ages at menopause (Table 5). In order to compare directly effects associated with each type of menopause, all risks were calculated in relation to women undergoing a natural menopause at ages 50–54. This was chosen as the referent category since the median age at natural menopause among this cohort of women was found to be 51.1 years (9).

A comparison of risks among the naturally menopausal women showed no substantial differences according to varying ages at natural menopause, although those with earlier menopause were at somewhat lower risk. In addition, no relationships were seen with age at menopause among those with a hysterectomy alone or a hysterectomy with unilateral oophorectomy. A significant trend, however, was observed according to increasing ages at bilateral oophorectomy, with those experiencing ovarian ablation at age 50 or later being at approximately a twofold excess risk compared to those with bilateral oophorectomy at a young age (<40 years). In addition, women experiencing a bilateral oophorectomy prior to the age of 45 were at 26–45% lower risk than those undergoing a natural menopause at ages 50–54, and at 16–20% lower risk than those undergoing a natural menopause at comparable ages. In contrast, a bilateral oophorectomy after the age of 45 was not associated with any reduction in risk relative to a natural menopause.

Effects according to varying ages at natural menopause were further examined according to the interval between cessation of menses and breast cancer diagnosis (Table 6). Within each interval category, there was some indication of increasing risk with later ages at natural menopause, although none of the trends were statistically significant. After adjustment for the interval since menopause, those with menopause after the age of 50 were at approximately a 20% higher risk than those with earlier menstrual cessation, with the trend in risk being statistically significant ($p = 0.04$).

In order to evaluate latency effects associated with a bilateral oophorectomy, risks by menopausal age and interval since oophorectomy were calculated in relation to women undergoing a natural menopause at ages 50–54 years (Table 7). Although numbers in this analysis became sparse, the importance of a latency effect in conferring protection was apparent. Women with less than a 15-year latency between oophorectomy at a young age (<45 years) and breast cancer diagnosis exhibited minimal protection relative to women undergoing a natural menopause at an average age. However, those with more than 15 years latency had significantly low risks (RRs = 0.2–0.5). In addition, after 15 years there was even some protection associated with oophorectomy at later ages (45+ years), although to a lesser degree than noted for the earlier operations.

Validation of Reported Gynecologic Operations

Table 8 shows the rate of agreement between the patient and hospital reports regarding the number of ovaries removed at the time of surgical menopause. As can be seen, the highest rate of agreement between patient and hospital reports was when patients reported that no ovaries had been removed (92.1% agreement). The lowest rate of agreement (81.6%) occurred when the patient

Table 5
Relative Risks[a] of Breast Cancer by Type of Menopause and Age at Menopause: All Risks Relative to Women with a Natural Menopause at Ages 50–54

Age at menopause	Type of menopause			
	Natural	Hysterectomy alone	Unilateral oophorectomy	Bilateral oophorectomy
<40	0.75 (42)[b]	1.07 (128)	0.93 (69)	0.55 (56)
40–44	0.90 (127)	0.90 (85)	1.00 (45)	0.74 (72)
45–49	0.83 (329)	0.88 (70)	1.05 (31)	0.99 (107)
50–54	1.00[c] (501)	0.95 (33)	1.04 (11)	1.02 (67)
55+	0.94 (120)	1.44 (6)	1.98 (2)	1.16 (16)
Trend test[d]	1.91	0.14	0.10	10.29
	(p = 0.17)	(p = 0.70)	(p = 0.75)	(p < 0.01)

[a]Relative risks are adjusted for age at diagnosis and years of menopausal hormone use.
[b]Numbers in parentheses represent number of cases.
[c]Referent group.
[d]Trend tests are derived by categorizing age at menopause within each type of menopause, using age <40 as the lowest score.

Table 6
Relative Risks[a] of Breast Cancer by Age at Natural Menopause and Interval Between Menopause and Breast Cancer Diagnosis

Age at menopause	Interval between menopause and breast cancer				
	<10	10–14	15–19	20+	All (adjusted)
<45	1.00 (27)[b]	1.00 (25)	1.00 (35)	1.00 (82)	1.00 (169)
45–49	1.17 (135)	1.06 (72)	0.90 (58)	0.96 (64)	1.01 (329)
50–54	1.51 (298)	1.12 (95)	1.10 (74)	1.41 (34)	1.26 (501)
55+	1.27 (78)	1.73 (30)	1.26 (12)	—	1.22 (120)
Trend test	1.97	1.74	0.47	0.33	4.33
	(p = 0.16)	(p = 0.19)	(p = 0.49)	(p = 0.56)	(p = 0.04)

[a]Relative risks are adjusted for years of menopausal hormone use. Total column is adjusted additionally for interval between menopause and breast cancer diagnosis.
[b]Numbers in parentheses represent number of cases.

Table 7
Relative Risks[a] of Breast Cancer Associated with Bilateral Oophorectomy by Age at Oophorectomy and Interval Between Oophorectomy and Breast Cancer Diagnosis

Age at oophorectomy	Interval between oophorectomy and breast cancer			
	<10	10–14	15–19	20+
<40	0.83 (10)[b]	0.56 (8)	0.16* (5)	0.55 (33)
40–44	0.85 (27)	1.95 (22)	0.37* (9)	0.34* (14)
45–49	1.10 (64)	1.09 (24)	0.71 (14)	0.29* (5)
50+	1.12 (58)	1.36 (16)	0.65 (6)	0.62 (3)
Trend test	0.87	5.83	0.85	0.89
	(p = 0.35)	(p = 0.02)	(p = 0.36)	(p < 0.34)

[a]All risks are relative to women undergoing a natural menopause at ages 50–54 within interval categories. Risks are adjusted for years of menopausal hormone use.
[b]Numbers in parentheses represent number of cases.
*p < 0.05.

Table 8
Rate of Agreement Between Patient and Hospital Reports Regarding Number of Ovaries Removed

	Patient reported number of ovaries removed	Hospital reported number of ovaries removed		
		0	1	2
Controls				
	0	47 (94.0)[a]	1 (2.0)	2 (4.0)
	1	2 (12.5)	13 (81.2)	1 (6.2)
	2	5 (8.1)	5 (8.1)	52 (83.9)
Cases				
	0	58 (90.6)	2 (3.1)	4 (6.2)
	1	3 (13.6)	18 (81.8)	1 (4.6)
	2	5 (7.4)	2 (2.9)	61 (89.7)
Total				
	0	105 (92.1)	3 (2.6)	6 (5.3)
	1	5 (13.2)	31 (81.6)	2 (5.3)
	2	10 (7.7)	7 (5.4)	113 (86.9)

[a]Numbers in parentheses are row percentages representing percent of patient reports regarding number of ovaries removed that were confirmed or disputed by hospital reports.

reported removal of only one ovary, and an intermediate rate of agreement (86.9%) when the patient reported removal of both ovaries. Cases and controls had generally similar agreement rates for the various operations reported.

DISCUSSION

The results of this study underscore the importance of menstrual factors in the etiology of breast cancer. Consistent with other studies, an elevated risk of breast cancer was associated with early menarche or late menopause, and a reduced risk was seen following bilateral oophorectomy.

It is noteworthy that we found a significant linear trend of reduced risk with increasing ages at menarche, particularly since some studies in North America (10–12) have failed to note such a relationship. The divergence of these results with those from several other countries, where more striking relationships with ages at menarche have been noted (1,13–16), has been attributed to the relative homogeneity of ages at menarche in North America. The size of our study population allowed sufficient variation in ages at menarche to demonstrate a 23% reduction in risk for women with menarche at age 15 or later compared to those with menses prior to the age of 12. We failed though to find a strong effect for age at menarche for the breast cancer cases with the earliest onset, as reported by others (1,12). Such differences may reflect better recall regarding ages at menarche among women who are closer in age to the event. However, it is of interest that we found little difference in the distribution of menarche across age categories nor did we find that older women more frequently provided unknown ages at menarche.

As an explanation for the inverse association of age at menarche with breast cancer risk, Korenman (17) proposed an estrogen window hypothesis that focuses on two main induction periods, the first prior to ovulatory menstrual cycles and the second during the perimenopausal period. He postulated that early establishment of regular ovulatory cycles would reduce susceptibility to tumor induction. Our findings, however, failed to support such an hypothesis. Similar to other studies (18–20), we found early menarche to be associated with earlier rather than later regularization of ovulatory cycles. We also observed no substantial differences between cases and controls with respect to intervals of irregularity after menarche, i.e., cases did not establish regular cycles later than controls. This differs from the study of Henderson et al. (18), in which cases established regular cycles significantly earlier than controls. In their study, women with early menarche and immediate establishment of cycles had almost a fourfold increased risk of breast cancer compared to women with late menarche and longer durations or irregular cycles. Our study failed to find any increased risk for those with early menarche and immediate regularization, possibly because our cases were significantly older than those included in the Henderson study (which focused on cases less than 33 years of age).

Our results further confirmed a higher relative risk (1.3) of breast cancer among premenopausal than menopausal women. We also observed a slightly higher risk for women undergoing a natural menopause at later ages, although those with menopause after the age of 54 had only a 20% increased risk relative to those whose menses ceased prior to the age of 45. This finding contrasts with a number of other studies (2–3,5,10–12) that have reported relative risks of approximately 2 for women with late menopause. Although age at natural menopause might be obscured by the high rates of menopausal estrogen usage in this population, we found no pronounced effect of age at menopause even when analyses were restricted to nonusers of hormones. Also, control for potential confounding variables did not alter the effects observed. We thus have no ready explanation for the comparatively small risk associated with late age at natural menopause in this population, other than the possibility of misclassification due to errors in recall (21), an issue of concern given the large number of older women in the study.

A reduced risk of breast cancer was noted among women with a surgical menopause that involved ovarian ablation, primarily when the operation occurred at a young age. Those with bilateral oophorectomy prior to the age of 40 had a 45% reduced risk compared to those with a natural menopause at ages 50–54, a finding consistent with previous investigations (3,22). The importance of ovarian ablation in reducing the risk of breast cancer was emphasized by finding that other types of surgical menopause were not associated with any lowering of risk. Further indication of a role for ovarian hormones was the risk differential between those with an early oophorectomy and those with the operation later in life. Consistent with findings of Trichopoulos et al. (3), there was a striking relationship of risk with increasing ages at oophorectomy, with those having an oophorectomy at ages 50 or later showing a twofold excess risk compared to those with the operation before age 40.

Although in general a bilateral oophorectomy exerted a protective effect on risk only when it occurred prior to the age at which natural menopause normally occurs, it was of interest that ovarian ablation at an early age was

somewhat more protective than a natural menopause at a comparable age. Thus, women with a bilateral oophorectomy prior to the age of 40 were at a 20% lower risk than those with a natural menopause at the same age, while women with surgery at ages 40–44 showed a 16% lower risk than naturally menopausal women. Although this observation has not previously been elaborated upon, it seems plausible that bilateral oophorectomy might exert a greater effect on risk than a natural menopause because of the more immediate and pervasive decline in endogenous hormones associated with surgery. Finally, these data were of interest in showing a clear latency effect associated with bilateral oophorectomy, with approximately a 15-year delay between the time of surgery and appearance of a reduction in breast cancer risk. This is consistent with findings of Trichopoulos et al. (3), as well as with observations that exogenous estrogens may exert their effects on breast cancer risk only after a substantial delay (23,24).

In interpreting these study results, several methodological issues warrant attention. Of particular concern was the larger proportion of cases than controls who had died prior to the time of our study. Although we are unaware of studies that have shown an effect of menstrual factors on survival, we attempted to evaluate a bias by analyzing separately women who were eligible for interview shortly after diagnosis from those who had longer intervals (and for whom the response rate was lower). This analysis showed similar effects of menstrual factors among both groups, providing reassurance that overall results were not affected to any significant extent by a survival bias. Of further concern was the possibility of recall bias, particularly since subjects were asked to supply information about many events in their distant past (e.g., onset of regular menses). Although we were unable to specifically evaluate such an effect, it was reassuring that the distribution of age at menarche was similar in younger as well as older women. In addition, it is noteworthy that the patient reports about types of surgical menopause accurately reflected information recorded in the medical records. Overall, the exact agreement rate for number of ovaries removed was 86%, with those who had no ovaries removed being able to provide the most accurate information (92% agreement). These results correspond well with those obtained by Weiss (25) who made comparisons between women with both or one/no ovaries removed; an overall agreement rate of 81% was noted, again with the most accurate information occurring among those women who did not have both ovaries removed. Hirayama and Wynder (5) found a lower agreement rate (57%), although based on small numbers of validated records. Although our higher agreement rates probably reflect to some extent an increased awareness regarding medical events on the part of women volunteering for periodic screening, it would appear from the available literature that patient reports can be used to assess accurately the relationship of menstrual factors to the risk of breast cancer.

In summary, our findings of increased breast cancer risk among those with early menarche or late menopause emphasize the importance of endogenous hormones in the etiology of breast cancer. Noteworthy was the fact that ovarian ablation lowered risk primarily when it occurred prior to the age that natural menopause would be expected to occur. These observations, together with the linear trends in risk with age at menarche and age at menopause, suggest that tumor-promoting effects of hormones operate throughout a woman's reproductive life.

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